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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P11104 PC		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2004/014016		International filing date (day/month/year) 08.12.2004	Priority date (day/month/year) 08.12.2003	
International Patent Classification (IPC) or national classification and IPC C12N5/02				
Applicant CELLARTIS AB et al.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> sent to the applicant and to the International Bureau a total of sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 21.06.2005		Date of completion of this report 07.02.2006		
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized Officer Teyssier, B Telephone No. +31 70 340-		



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/014016

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-24 as originally filed

Claims, Numbers

1-16 as originally filed

Drawings, Sheets

1-10 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify)*:
 - ☐ any table(s) related to sequence listing *(specify)*:
 4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify)*:
 - ☐ any table(s) related to sequence listing *(specify)*:

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-16
	No: Claims	-
Inventive step (IS)	Yes: Claims	1-16
	No: Claims	-
Industrial applicability (IA)	Yes: Claims	1-16
	No: Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

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(SEPARATE SHEET)**

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Reference is made to the following documents:

- D1 Amit M et al., *Developmental Biology* 15 November 2000, 227(2), 271-278
- D2 WO 03/055992 A (Cell Therapeutics Scandinavia AB) 10 July 2003
- D3 Pickering S J et al., *Reproductive Biomedicine Online* October 2003, 7(3), 353-364
- D4 Reubinoff B E et al., *Nature Biotechnology* April 2000, 18(4), 399-404
- D5 Xu C et al., *Nature Biotechnology* October 2001, 19(10), 971-974
- D6 Heins N et al., *Stem Cells* May 2004, 22(3) 367-376

Re Item II

Priority

The priority date of 8 December 2003 can be acknowledged for subject-matter deriving from present examples 1-5, 7 and 8, except those parts relating to clones of the SA002 cell line. Consequently, D6, a publication of the invention, does not belong to the state of the art under Rule 64 PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1 reports on the first clonal derivation of human embryonic stem cells (hES, a designation synonymous with "blastocyst-derived stem cells"; this Authority observes that the inventors used "hES" and not "hBS" in their publication D6). In the protocol of D1, regarded as the closest prior art, colonies are dissociated using collagenase (p. 272, top of right-hand column).

D3 reports on the derivation of a new hES cell line. In the derivation protocol, colonies are mechanically cut for derivation (p. 355, right-hand column), but are not dissociated in this way into single cells. Regarding the preparation of the hES themselves, reference is made to D4, in which "colonies [are] propagated in clumps of ~100 stem-like cells." (p. 403, right-hand column) Thus it appears that hES were not derived down to single cell clones in either D3 or D4.

D2 and D5 provide further background art on, respectively, the preparation of (non-clonal) hES from blastocysts and feeder-free growth of hES in Matrigel™.

The subject-matter of claim 1 is new and not obvious in view of the prior art (Article 33(2,3) PCT), since no method of clonal derivation of hES involving non-enzymatic treatment has been reported and the prior art fails to teach or even suggest that hES clumps could be dissociated into single cells solely by use of non-enzymatic means. Mechanical dissociation of hES clumps, as used in D3 and D4 does not yield single cells and, as such, would be unsuitable to replace collagenase digestion in the protocol of D1; there is no suggestion to add further non-enzymatic steps, such as the use of a chelator. Claims 2-16 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to

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novelty and inventive step.